



APV FOCUS GROUP DRUG DELIVERY

COMBINING SCIENCE & TECHNOLOGY TO CREATE ADVANCED DRUG DELIVERY SYSTEMS

INTERNATIONAL ASSOCIATION FOR PHARMACEUTICAL TECHNOLOGY

NEWSLETTER

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DRUG DELIVERY EVENTS

Provided by Christoph Blümer

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Oral Multiparticulate Dosage Forms – What's new?

November 13 – 14 2012, Prague, Czech Republic

[Details](#)

◇ New APV Course "Drug Delivery Strategies for Poorly Water Soluble Drugs - Established Platform Technologies & Recent Innovations"

November 29-30, 2012, Braunschweig, Germany

Despite one decade of intensive scientific discussion and global conferences on the subject of poorly soluble compounds, today there is still a strong need to understand better the principles underlying special types of formulation, their preparation and screening, variant selection based on biopharmaceutical criteria, stability prediction and in-depth material science aspects.

[Details](#)

The new APV course, which will be held in Braunschweig on November 29-30, will be chaired by Dr. Oskar Kalb and Dr. Carsten Timpe from Hoffmann-La Roche AG, Basel, Switzerland. In addition to nanotechnology aspects (nanomilling, screening tools for stable nanosuspensions and downstream processing), it will focus on the parenteral drug delivery of poorly soluble drugs and also on other new technologies and innovative analytical approaches to prepare and characterize these systems in order to improve the biopharmaceutical properties of challenging new compounds. One course highlight will be a visit to the innovative nanomilling facility at the Institute for Particle Technology (Technical University Braunschweig, Prof. Arno Kwade).

◇ APV Course 6475: Successful Early Stage Development of Pharmaceuticals

March 5-6, 2013 Rhine-Main area, Germany

Chairs: Mathew Leigh, Phares AG, Basel (CH); Louise Rosenmayr-Templeton, Tower Pharma Consulting, Vienna (A)

This course will guide participants through the challenges and pitfalls of early drug development from candidate identification and selection to developing formulations for animal studies and Phase I trials. It will examine the issues from both a Big Pharma and small company perspective. Topics covered include the realities faced when selecting a lead candidate and how to improve the chances of success, the physicochemical characterisation of drug compounds and strategies for overcoming problems such as poor water - solubility when formulating for pre-clinical, toxicology and Phase I.

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[Suggest a meeting to be announced!](#)

QUILLIVANT™ XR (NextWave Pharmaceuticals, Inc.)

On 27.9.2012 the FDA approved QUILLIVANT™ XR, an extended release formulation of methylphenidate hydrochloride which after reconstitution with water forms a 25mg/5ml suspension for oral administration [1]. It is indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD). Approval was based on a 2-week, placebo-controlled, double-blind, laboratory classroom trial in 45 children aged 6-12 years with ADHD together with data from previous clinical trials which evaluated the ability of this drug to control ADHD. In addition to the clinical study, the pharmacokinetics of the new formulation were assessed in adults, adolescents and children. The formulation is based on Tris Pharma Inc's OralXR+ platform [2] technology and contains approximately 20% immediate-release and 80% extended-release methylphenidate particles which are around 100 microns in diameter. The OralXR+ technology involves complexing the drug with a pharmaceutically acceptable ion-exchange resin (in the case of methylphenidate hydrochloride, sodium polystyrene sulfonate). The sustained release particles consist of these complexes embedded in a polymer matrix which is then coated with a cured, flexible, water-insoluble, water-permeable coating based on polyvinyl acetate. The immediate release particles consist of uncoated drug-resin complexes [3]. The formulation provides therapeutic plasma levels of methylphenidate hydrochloride for 12 hours. The recommended starting dose of QUILLIVANT XR is 20 mg once daily in the morning with or without food but the dose should be titrated to meet the patient's needs up to a maximum of 60 mg per day [1].

The approval represents another success for the collaboration between NextWave and Tris Pharma, the first being Nexiclon™XR, an extended-release tablet and suspension formulation of clonidine (launched in the US in 2010) [4]. Under the collaboration agreement NextWave is responsible for commercial activities involving QUILLIVANT™ XR, while Tris will manufacture the product at its New Jersey facility.

Flutiform® (Skye Pharma)

On 3 July 2012 Skye Pharma finally received approval for its Flutiform® metered dose inhaler for asthma maintenance therapy in 21 countries in Europe [5, 6]. The inhaler contains fluticasone propionate (fluticasone) and the long-acting β_2 agonist, formoterol fumarate. Formoterol is moisture-sensitive and so the product utilizes the company's SkyeDry™ technology [7] in order to improve the drug's stability.

The product was originally submitted for review through the decentralized route using the UK as reference member state. However it was referred to the Committee for Human Use (CHMP) after the Dutch authorities raised concerns about the long-term efficacy of the product. These concerns were based on data showing that blood levels of fluticasone propionate following dosing with Flutiform were lower than when fluticasone propionate was administered alone.

At their April meeting the CHMP concluded that the benefits of the product outweighed the risks [8]. The product will be marketed by Mundipharma International Limited in Europe [5] and at the time of writing this article it had been already launched in the UK and Germany [9].

References and Further Information

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DRUG DELIVERY COMPANIES

Provided by Jeffrey Grunkemeyer

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IOTA NANOSOLUTIONS LIMITED (Liverpool, UK)

IOTA NanoSolutions has developed ContraSol™, a novel nanoparticle generation technology for the enhanced formulation of low solubility compounds. ContraSol™ offers opportunities to enhance the performance of marketed drugs, NCEs and drug candidates currently in development and to revive promising discovery compounds previously overlooked owing to inadequate aqueous solubility.

Fact sheet:

Founded:	IOTA NanoSolutions Limited was registered as a spin out company from Unilever, UK, in 2005
Location:	MerseyBIO, Crown Street, Liverpool, L69 7ZB, UK
Ownership:	IOTA NanoSolutions is currently funded by Unilever Ventures Limited (a venture capital firm providing funding and management skills to start-up and early stage businesses) and QIB (UK) Plc (the UK subsidiary of Qatar Islamic Bank). Minority stakes in IOTA NanoSolutions are also owned by the founder Directors and the University of Liverpool.
Employees:	15
Key technology:	<p>ContraSol™: a novel 'bottom up' approach to generating nanoparticles and enhancing solubility kinetics of low solubility compounds</p> <p>IOTA NanoSolutions addresses the challenge of improving the sub-optimal and physiochemical properties often associated with BCS Class II and Class IV compounds by enhancing drug solubility/dissolution kinetics through its patented particle formation technology ContraSol™.</p> <p>The ContraSol™ technology produces a dry, solid blend of low solubility compound as nanoparticles embedded within a soluble matrix. When added to liquid, the soluble matrix rapidly dissolves to liberate the low solubility compound as a nanoparticulate dispersion with a typical Zave (hydrodynamic diameter) of 100-300nm. High loading is a key feature of the ContraSol™ technology and formulations containing up to 85wt% of the low solubility compound have been achieved.</p> <p>The ContraSol™ technology forms nanoparticles from a molecular solution in a 'bottom up' approach. The process relies upon evaporative removal of solvent and water from the system which in turn results in the controlled precipitation/crystallisation of nanoparticles of low solubility compound within an excipient matrix:</p> <ul style="list-style-type: none"> • Step 1, The low solubility compound and excipients are dissolved in a common solvent system (comprising one or more miscible solvents) to form a 'single solution' or they are dissolved in separate immiscible solvents to form an emulsion system • Step 2, The resulting feedstock liquid is dried with the process solvent(s) removed (and recovered) from the final solid product. Drying techniques may include modified freeze drying, spray drying or spray granulation approaches. • Step 3, When the solid product is added to a liquid, a nanodispersion of the low solubility compound is created as the excipient matrix (in which the particles have been formed) dissolves. <p>The ContraSol™ technology is not constrained by the physical chemical properties of the low solubility compound and can be applied to amorphous, crystalline, low melting point and temperature sensitive materials. In contrast to other 'top down' techniques such as milling, the ContraSol™ technology avoids the use of harsh physical conditions thus overcoming the potential to generate contaminants during processing.</p> <p>Soluble matrices present in the custom formulations are selected from commercially available pharmaceutical grade excipients that are already present in approved products. The resultant dry, redispersible solids can be directly incorporated into solid and liquid formats and have demonstrated enhanced efficacy and bioavailability in a range of <i>in vitro</i>, <i>ex vivo</i> and <i>in vivo</i> models</p>

	<p>when compared to equivalent solvent solutions and conventional formulation approaches. Key features and clinical benefits/opportunities include:</p> <p>Oral candidates</p> <ul style="list-style-type: none"> • Bioavailability enhancement (reduce dose, patient variability, food effects and side effects) • High drug loading (reduce pill size/burden, improve patient compliance) • Output is a redispersible solid (new product formats, e.g. sachets, soluble tablets) • Incorporate multiple low solubility compounds into the nanoparticle (fixed dose combinations) <p>Parenteral candidates</p> <ul style="list-style-type: none"> • High drug loadings (high dosed aqueous systems) • Alternative to cyclodextrins and co-solvents (reduce sides effects, improve patient compliance) • Output is a redispersible solid (improve shelf life following 'point of use' concept) • Incorporate multiple low solubility compounds into the nanoparticle (fixed dose combinations)
Products:	IOTA NanoSolutions has multiple joint development agreements in place with large and small-mid sized pharmaceutical R&D companies for evaluation of ContraSol™ formulations in NCE development and product lifecycle management settings. The most advanced ContraSol™ formulation is currently in pre-clinical studies and first in man data is expected within the next 12-18 months.
Development status:	The ContraSol™ technology makes use of industry standard equipment and is readily scalable. ContraSol™ formulations have already been successfully transferred to cGMP manufacture.
Partnerships:	In addition to collaboration with industry partners, IOTA NanoSolutions maintains an ongoing relationship with the University of Liverpool to support research of antiretroviral nanomedicine therapies for HIV/AIDs and is currently developing an internal R&D pipeline of drug candidates for progression to a clinical setting and onward licensing.
Website:	http://www.iotanano.com
Contact:	<p>Christopher Young, Business Development Director Dr Alison Foster, Pharmaceutical Programme Director IOTA NanoSolutions, MerseyBIO, Crown Street, Liverpool, L69 7ZB, UK Phone: +44 (0)151 795 4219 Fax: +44 (0)151 795 4173 e-mail: info@iotanano.com</p>

DRUG DELIVERY PEOPLE

Provided by Prof. Dr. Karsten Mäder

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JENNIFER DRESSMAN is Professor of Pharmaceutical Technology and Director of the Institute of Pharmaceutical Technology at the Goethe University in Frankfurt am Main, Germany. She received her B. Pharm degree in Pharmacy from the Victorian College of Pharmacy, Melbourne in 1976 and her Ph.D. in 1980 from the University of Kansas in the USA under the direction of Prof. Takeru Higuchi. From 1980 to 1983 she held positions as Senior Scientist at Burroughs Wellcome and Interx/Merck before joining the Pharmaceutics Faculty at the University of Michigan (USA) as an Assistant Professor. In 1989 she was promoted to Associate Professor, with tenure, at the same university and in 1994 took up her current position.

Jennifer's research interests focus on predicting the *in vivo* performance of drugs and dosage forms after oral administration. To this end she spent many years at the University of Michigan and in close collaboration with Prof. Dr. Christos Reppas at the University of Athens in Greece characterizing the conditions in the gastrointestinal (GI) tract. Based on these studies they have developed biorelevant media to reflect conditions in the stomach, small intestine and colon, enabling formulators to test release from prototype dosage forms *in vitro* under conditions corresponding to all areas in the GI tract. Over the last few years, she has worked on coupling results from biorelevant dissolution tests with physiologically based pharmacokinetic (PBPK) models with the aim of quantitatively predicting plasma profiles after oral drug administration, a so-called *in vitro-in silico-in vivo* (IVISIV) approach to correlation.

Additionally, Jennifer is Director of the WHO Collaborating Center for Research on Bioequivalence. This Center has the aim of improving the availability of quality medicines globally through appropriate bioequivalence testing. A large part of this work involves preparing Biowaiver Monographs (www.fip.org/bcs_monographs) but also encompasses designing appropriate quality control tests for drugs on the Essential Medicines List. In accord with these activities, she is Chair of the Focus Group BCS and Biowaiver of the FIP.



Jennifer's research has been recognized by several awards, including the *Ebert Prize* (1987), *Fellowship in the AAPS* (1991), *Phoenix Prize* (2003), the *Distinguished Scientist Award* of the FIP (2008), *Fellowship in the CRS* (2010) and the *Best Paper Award* for 2010 from the European Journal of Pharmaceutics and Biopharmaceutics. She is co-author of more than 200 peer reviewed papers and book chapters, five books and thirteen patents and is the principal advisor of 43 completed Doctoral Theses.

OCULAR DRUG DELIVERY

This newsletter section is intended to give a brief overview of academic groups based at European Universities working on ocular drug delivery. It is the second of an occasional series reviewing the work of research teams exploring different aspects of drug delivery research. It is not intended to be a comprehensive list of those involved in the area but give our readers a flavour of the type of research being carried out at European Universities. As it is a living document, our readers are most welcome to suggest other European academic ocular delivery research teams they are aware of for inclusion in our next edition.

Helsinki, Finland

Institute	Centre for Drug Research, Faculty of Pharmacy, University of Helsinki
Group	Drug Delivery and Nanotechnology
Key Contact	Prof. Dr. Arto Urtti
Website	http://www.helsinki.fi/cdr/research/group_urtti.htm
E-mail	Arto.urtti@helsinki.fi
Research Areas	<ul style="list-style-type: none"> • Ocular pharmacokinetic modelling, • Cell models and cell therapy, • Nanoparticle mediated drug delivery

Paris, France

Institute	Universite Paris Descartes
Group	Institute Biomedical des Cordeliers
Key Contact	Prof. Dr. Francine Behar-Cohen
Website	http://www.crcjussieu.fr/crc/index.php?cible=projet_equipe&id=17&spgmGal=equipas/17
E-mail	francine.behar-cohen@crc.jussieu.fr
Research Areas	<ul style="list-style-type: none"> • Particulate drug delivery systems for intraocular drug delivery • Ocular iontophoresis • Electroporation • Non-viral gene delivery • Protein delivery • Implants • Supra choroidal delivery

Greifswald, Germany

Institute	Ernst-Moritz-Arndt-Universität
Group	Institut für Pharmazie Biopharmazie & Pharmazeutische Technologie
Key Contact	Prof. Dr. Werner Weitschies
Website	http://pharm1.pharmazie.uni-greifswald.de/Techno/index.htm
E-mail	werner.weitschies@uni-greifswald.de
Research Areas	Development of biorelevant models for the characterization of topical ocular and intraocular drug delivery systems for the eye.

Nijmegen, The Netherlands

Institute	Radboud University, Faculty of Science
Group	Bio-organic Chemistry
Key Contact	Prof. Dr. Jan van Hest
Website	http://www.ru.nl/bio-orgchem/people/current_group/prof_dr_ir_jan_c_m/
E-mail	j.vanhest@science.ru.nl
Research Areas	<ul style="list-style-type: none">Elastomer delivery systems for the eye

Glasgow, Scotland

Institute	University of Strathclyde, Glasgow
Group	Strathclyde Institute of Pharmacy and Biomedical Sciences
Key Contact	Prof. Dr. Clive Wilson
Website	https://pure.strath.ac.uk/portal/en/organisations/strathclyde-institute-of-pharmacy-and-biomedical-sciences(a2d0d1ee-5c6b-47d4-9a69-9559a744e3be).html
E-mail	c.g.wilson@strath.ac.uk
Research Areas	<ul style="list-style-type: none">Implants for ocular drug deliveryFinite element modeling of drug distribution in the eyeBiopharmaceutics and formulation research

Madrid, Spain

Institute	Complutense University, School of Pharmacy,
Group	Department of Pharmacy and Pharmaceutical Technology,
Key Contact	Prof. Dr. Rocio Herrero-Vanrell
Website	http://portal.ucm.es/en/web/en-ucm/research
E-mail	rociohv@farm.ucm.es
Research Areas	<ul style="list-style-type: none">Microparticles for drug delivery to the back of the eyeNew biomaterials for ophthalmic administrationOphthalmic drug delivery systemsOptimization of ophthalmic formulations

Santiago de Compostela, Spain

Institute	University of Santiago de Compostela
Group	Department of Pharmaceutical Technology
Key Contact	Prof. Dr. M. J. Alonso
Website	http://webspersoais.usc.es/persoais/mariaj.alonso/cvmj.html#edu
E-mail	mariaj.alonso@usc.es
Research Areas	<ul style="list-style-type: none">Transport of nanostructures across the ocular mucosa to improve the transport of drugs across the cornea as well as to facilitate the internalization of genes in the cornea and conjunctiva.

Valladolid, Spain

Institute	University of Valladolid
Group	IOBA, Institute for Research in Applied Ophthalmobiology
Key Contact	Dr. Yolanda Diebold
Website	www.ioba.es
E-mail	yol@ioba.med.uva.es
Research Areas	<ul style="list-style-type: none">• Development of new therapeutic strategies to treat ocular inflammatory diseases:• Topical drug delivery systems• Mucoadhesive molecules• Biopolymers for 3D tissue reconstruction and functional recovery

Geneva, Switzerland

Institute	University of Geneva
Group	Pharmaceutical Technology
Key Contact	Prof Dr. Robert Gurny
Website	http://www.unige.ch/sciences/pharm/fagal/page-perso/Gurny.php?id=22
E-mail	Robert.Gurny@unige.ch
Research Areas	<ul style="list-style-type: none">• Pharmaceutical formulations for ocular use• Biodegradable polymers• Nanoparticles• Protein and peptide delivery, gene therapy• Controlled release

Durham, United Kingdom

Institute	University of Durham, UK
Group	Department of Chemistry
Key Contact	Prof. Dr. Neil Cameron
Website	http://www.dur.ac.uk/n.r.cameron/
E-mail	n.r.cameron@durham.ac.uk
Research Areas	<ul style="list-style-type: none">• Self assembling peptide-based nanoparticles for sustained drug delivery to the posterior segment of the eye

London, United Kingdom

Institute	University of Kingston
Group	--
Key Contact	Prof. Raid Alany
Website	http://sec.kingston.ac.uk/about-SEC/people/academic/view_profile.php?id=2015
E-mail	r.alany@kingston.ac.uk
Research Areas	<ul style="list-style-type: none">• Ophthalmic Drug Delivery• Lipid and Surfactant Based Drug Delivery Systems• Delivery of Antisense Oligonucleotides and siRNA• In Situ Gelling Systems

Drug Delivery Systems Used To Deliver Opioids in Chronic Pain Therapy

Part II: Transdermal Systems

By Johannes Bartholomäus, Burghöhenweg 5, 52080 Aachen

3. Transdermal formulations

Technical solutions by drug delivery systems

This article is the second in a series dealing with drug delivery systems used to deliver opioids in chronic pain therapy. The first of these articles appeared in the Feb 2011 issue of the Newsletter and covered oral prolonged release systems. Since oral formulations have a maximum dosing interval of about once daily, there was a need in chronic pain treatment for convenient drug delivery systems which allowed a longer duration of action. This became technically feasible when transdermal patches were invented at the end of the 1970s, beginning of the 1980s. As human skin is more a barrier of the body against the environment as opposed to an absorption organ, drug substances need to have particular physico-chemical properties and specific formulations to become transdermally bioavailable. Only opioids that have the right lipophilic-hydrophilic balance can pass through the lipophilic skin barrier and also be transported in the aqueous environment of the body. Since for most compounds only low doses are able to cross the skin, this route of delivery is limited to highly potent compounds. A lot of the classical opioids need much higher doses per day than could pass the skin and, thus, only few very potent opioids like fentanyl, its derivatives (sufentanil etc.) and buprenorphine are suitable for passive transdermal administration. Prior to the development of transdermal patches, these opioids were not used in oral chronic pain treatment because of their high and variable first-pass effect. Fentanyl was only available as an injection and buprenorphine as an injection and sublingual tablet.

In the 1980s ALZA started development on a fentanyl transdermal system based on a reservoir patch (Fig. 1). The system consisted of a polyester film backing membrane and an ethylene-vinyl acetate copolymer release controlling membrane forming a pouch that was filled with a solution/suspension of fentanyl in a water-ethanol mixture gelled by hydroxyethyl cellulose. The silicon adhesive layer also contained fentanyl from equilibrium of the system between this layer and the drug reservoir. The final protective liner had to be detached just before administration.

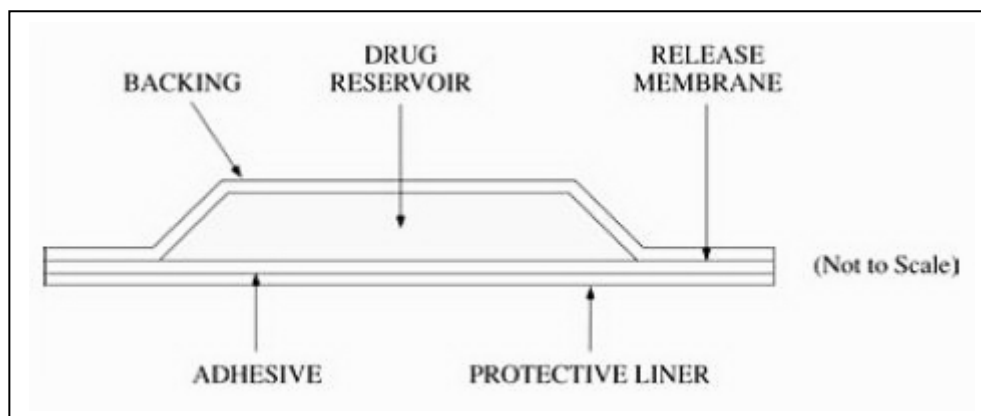


Fig. 1 Scheme of fentanyl reservoir patch (Source: Duragesic[®] Label, 2005)

The composition of the drug formulation and the release membrane together control the drug flux (amount of drug absorbed per unit time and area) of the fentanyl through the skin. By multiplying the drug flux with the active release area of the patch the dose administered per time to the body can be determined. The delivery of drug from a patch system is therefore not characterized by the dose in the patch but by the administration rate per hour. The initial Duragesic[®]/Durogesic[®] patches offered a flux of about 25 µg/h per 10 cm² and delivered 25, 50, 75 and 100 µg/h by adjustment of the release area. Later a 12.5 µg/h patch was added. Different dose strengths are necessary as, like with oral opioids, the therapeutic dose has to be titrated until sufficient pain relief is achieved. Alternatively, the dose required can be calculated through knowledge of the effective individual oral dose of another opioid and the therapeutically equivalent fentanyl transdermal dose. The patches were designed for a 3-day treatment period characterized by relatively constant blood concentrations over the 3 days with a small decline on the last day. The fentanyl patches were introduced by Janssen, a subsidiary of Johnson&Johnson, to the market in the US in 1990 and in Europe 1995. Over time the product became well accepted by physicians and patients as they provided a real therapy advantage first in cancer pain and later also in benign chronic pain. Duragesic[®]/Durogesic[®] grew to the most successful transdermal product ever in terms of sales with peak sales of about 2 Billion USD.

A disadvantage of the liquid-filled reservoir patch design is the risk of leakage. Such leakage occurred in some batches of fentanyl patches in the 2000s releasing fentanyl from the patch in an uncontrolled manner resulting in potential over-

dosing. Thus, from mid of the 2000s onwards the reservoir patch design was replaced by a new drug-in-adhesive design under the name Duragesic®/Durogesic® SMAT consisting of a backing layer, a drug containing adhesive polyacrylate matrix layer and a protective liner. In these systems the control of drug release is in the design of the matrix formulation. The new SMAT patches are bioequivalent to the reservoir patches based on equivalence of serum concentration curves (C_{max} and AUC). The administration rate per hour also remains the same although the formulation of the patch was changed including an 68% increase in the total amount of fentanyl in the patches e.g. the 25 µg/h reservoir patch contained 2.5 mg fentanyl in total whereas the SMAT patch has 4.2 mg fentanyl. A peculiarity of transdermal patches is that the use of different amounts of active can lead to identical dose rates (µg/h) due to the different thermodynamic activities of the active in the environment of the different formulations. Every transdermal patch needs an excess of drug remaining in the patch at the end of the dosing interval to assure a constant release rate during therapy. Different formulations often lead to different extents of utilization of the amount of drug employed per patch. This becomes particularly evident when comparing different fentanyl patches after the introduction of generics in the mid of the 2000s (see examples of 25 µg/h patches on the German market (Table 1)). All patches achieved marketing authorization by proving bioequivalence.

Table 1: Comparison of total drug load, utilization of drug load and release area of fentanyl patches of German market (Durogesic® Reservoir is not available anymore and was replaced by SMAT)

	Durogesic® Reservoir	Durogesic® SMAT	Generic 1	Generic 2	Generic 3	Generic 4	Generic 5
Fentanyl per patch	2.5 mg	4.2 mg	2.75 mg	4.8 mg	5.1 mg	2.75 mg	4.1 mg
Utilized after 3 days	72 %	43 %	65 %	38 %	35 %	65 %	44 %
Release area	10 cm ²	10 cm ²	10 cm ²	15 cm ²	8.5 cm ²	8.4 cm ²	7.5 cm ²

The highest drug load utilization was achieved by the classical reservoir formulation with release controlling membrane but which has the risk of leakage. The generics with high utilization close to the reservoir patch are made of silicon matrices in combination with a rate controlling membrane and an adhesive layer, while the SMAT formulation and the other generics with the lower utilization are made as pure drug-in-adhesive designs with polyacrylate matrices. Nowadays, regulatory bodies compare new abridged marketing authorization applications for patch generic products to state-of-the-art formulations already approved. As an example, an application for a bioequivalent fentanyl patch (25 µg/h) with a total drug load of 9.2 mg and a utilization of 19.5 % was considered not approvable by the CHMP. Further reasons for the decision were the large patch size compared to the reference product and problems in adhesion and skin irritations. Therefore in order to be approved as a generic, patches must not only contain the identical active substance and show bioequivalence in terms of AUC and C_{max} , but also should have the same skin tolerability, the same adhesive properties – as contact between the drug release area of the patch and the skin is critical for bioavailability – and a comparable patch size as well as an excess of total drug load not much above that of comparable products.

Buprenorphine is the only other opioid developed for transdermal administration that has up to now reached commercialization. Compared to fentanyl the molecular weight of buprenorphine is higher and its melting point is considerable higher (88°C vs. 209°C). Following a rule of thumb, transdermal administration of buprenorphine because of these properties may face some more hurdles than fentanyl. The technical challenges of buprenorphine patches were overcome by LTS Lohmann as the drug delivery system provider using a subcooled matrix formulation enabling a high concentration of dissolved drug. Grünenthal in Europe conducted the clinical development and commercialization of this product achieving the first marketing authorization for a buprenorphine patch (Transtec®) in 2000. Purdue Pharma developed the product for the US (Butrans®) with approval in 2010. The product is designed as a drug-in-adhesive patch – already before the first fentanyl patches used this technology. The patch has a peculiar design in that the rectangular drug containing adhesive matrix is placed onto a somewhat larger adhesive patch with rounded edges with both layers separated by an impermeable membrane. Such design enables on the one hand less narcotic waste for the buprenorphine laminate and on the other hand proper adhesion to the skin. The first dose strengths reaching market had administration rates of 35, 52.5, and 70 µg/h (25, 37.5, and 50 cm² active release area). The patches allow for a dosing interval of 4 days enabling also the possibility of fixing two defined days of the week as the “patch change days” if one patch is used for 4 days of the week and the other for the remaining 3 days or vice versa. This may simplify administration schedules for both patients and carers. Later the portfolio was extended to lower administration rates of 5, 10, and 20 µg/h suitable for once weekly dosing. In the US Purdue Pharma markets the once per week 5, 10, and 20 µg/h patches.

By the end of the 2000s the first generic buprenorphine patches with 35, 52.5, and 70 µg/h designed as drug-in-adhesive entered the market in Europe. Sizes, total drug load and utilization are the same as for the reference product.

In the 2000s two drug delivery companies, Labtech – now a tesa-company – and Durect, independently started the development of sufentanil patches trying to establish a third transdermal opioid. Both products are designed as drug-in-adhesive patches allowing for about 3 days dosing interval with the Labtec product and 7 days for Durect’s patch. Both products have been taken to Phase II studies with Labtec running the program with a CRO and Durect with a licensee for marketing in the US. The licensee later returned the rights to the product to Durect,. Hence, both products seem to be open for licensing.

A different formulation approach for transdermal administration of fentanyl was explored by the Australian drug delivery company Acrux using precisely metered liquid spray-on-skin formulations containing permeation enhancers derived from sunscreen molecules which formed a "patchless patch" on the skin. Although phase I trials revealed bioequivalence to Duragesic® no commercial partner came on board to take the product forward to market. On the other hand the technology itself made it to market e.g. for a variety of sex hormone products.

Passive patches based on diffusion of drug substances through the stratum corneum are not suitable to deliver higher amounts of opioids or more hydrophilic opioids. Poration of the stratum corneum with microneedles or thermal ablation by a laser or controlled heat applied for a few microseconds form holes and hydrophilic channels that allow larger amounts of hydrophilic drugs to enter the body. For example, with the Altea Passport® system once daily administration of hydromorphone via the skin has been demonstrated but also in this case no partner for development and commercialization of the product could be found.

The only non-passive diffusion based transdermal opioid product that reached the market was the Ionsys® system which used active transport by iontophoresis to deliver fentanyl. It was indicated for postoperative acute pain (not chronic pain) and was for patient controlled analgesia (PCA). Like with a PCA infusion pump the patient could self-administer bolus doses of fentanyl by pushing a button to activate the electric field transporting the drug through the skin via hydrophilic pathways. This iontophoretic administration delivered practically identical blood concentration profiles as a fentanyl PCA infusion pump while having the advantage of no infusion tubing etc. The marketing of the product was stopped after some malfunctions of the iontophoretic system which seemed to be due to corrosion.

From Technical Solutions to Commercial and Environmental Factors and back

After oral prolonged release formulations of opioids had pioneered the commercial success of analgesics in treatment of chronic pain it seemed to be a logical step to add therapeutic options allowing longer dosing intervals. However, the process still took time and involved overcoming technical challenges as well as educating healthcare staff and patients before the first transdermal opioid patch reached the market and gained popularity. The first key to success was in the selection of a known short acting opioid practically only used as an injection in hospital settings and repurposing it for chronic pain treatment by a new way of administration. The second key was in educational programs teaching on the peculiarities of transdermal treatment starting with points like defining doses in administration rates ($\mu\text{g}/\text{h}$) instead of fixed amounts (μg or mg) per dosage form but also including safety information. For example many people have a positive attitude towards transdermal patches because they remember from childhood that pain already seem to disappear after their mother put an adhesive plaster on the wound. Nevertheless it has always to be borne in mind that regardless of the route of administration, overdosing of opioids has serious side effects especially respiratory depression, particularly in opioid naïve patients and tolerant patients who get more patches than prescribed, change patches too frequently or expose them to heat sources. This was pointed out in FDA warnings in 2005 and 2007 after reports of death and life-threatening adverse events. From such warnings it can be derived that although fentanyl patches have been marketed for years the need for the education of patients, caregivers and physicians is still there and may even need to be extended given the growth in the generics market. For example it is said that administration from the patch can be interrupted by removing it in case of adverse events. However, it needs to be considered that some drug is still delivered by subdermal depots which continue to release after patch removal. Externally applied heat e.g. by hot-water bags or hot showers as well as "internal heat" as a result of fever may increase the administration rate of drug to the body by higher thermodynamic activity of the drug in the patch, higher flux through the skin, and more intensive capillary blood circulation through the subdermal depot. These thermal effects on administration by patches were the basis for the development concept of Titragesia® in the 2000s which aimed to treat pain peaks in patients treated with fentanyl patches by short time application of controlled heat onto the patch (CHADD: Controlled Heat Aided Drug Delivery) to increase blood concentration of fentanyl for short time. The concept seemed to have been abandoned.

Another key for the success, especially of Duragesic®/Durogesic®, was the broad patent protection ALZA could achieve for an established compound in the still early times of transdermal drug delivery. It covered not only practically all transdermal use of fentanyl but also of its derivatives e.g. sufentanil in pain treatment. Thus, only very few other opioids suitable for transdermal pain treatment remained for potential competing products and from those only buprenorphine made it to the market. The broad fentanyl and derivatives patents expired a few years ago and therefore the way to e.g. more potent fentanyl derivatives' patches is now open. Despite this there appears to be few developments in this area. A hurdle on the way to commercialize e.g. sufentanil patches in the competitive environment of fentanyl generics might be that the main differentiation to distinguish the new patches from fentanyl patches is just the higher potency of the active, perhaps a smaller patch size and a once weekly administration interval, while the pharmacological profile is quite similar to fentanyl. Hence, the next transdermal analgesic products in treatment of chronic pain might need potent and selective actives with an improved safety profile and less potential for adverse events.

This featured article is Part 2 of a series and will be continued with a look at delivery systems with even longer application periods like implants as well as delivery systems for breakthrough pain in one of the next issues of the Drug Delivery Newsletters.

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COMBINING SCIENCE AND TECHNOLOGY TO CREATE ADVANCED DRUG DELIVERY SYSTEMS

OUR MISSION STATEMENT:

Modern drug delivery research and development is a truly multidisciplinary approach and must combine all relevant scientific, technical, medical and regulatory aspects required for the design, preparation, testing, manufacturing and registration of drug delivery systems and their components. It is the mission of the APV Drug Delivery Working Group to foster and promote all aspects of research and development required to transform drug molecules into safe, applicable and acceptable drug delivery systems, which provide therapeutic benefit, convenience to the patient and improve patient compliance.

Our mission includes in particular the following tasks:

- Thoroughly understanding the physical-chemical and biopharmaceutical properties of the drug substance to be delivered and the components of the drug delivery system
- Understanding the biological barriers and the interactions of the drug molecule and its delivery system with the biological environment and the biological target including PK/PD and PK/safety relationships
- Research on excipients, materials and technologies required for the design, preparation and manufacturing of drug delivery systems for a selected route of administration
- Development and understanding of methods for in vitro and in vivo evaluation of drug delivery systems and their components
- Knowledge of regulatory requirements for clinical testing, manufacturing and registration of drug delivery systems

All disciplines relevant to the above mentioned areas of drug delivery R&D are invited to contribute to the APV Drug Delivery Group:

Pharmaceutics, Biopharmaceutics, Analytics, Biology, Physical Chemistry, Biochemistry, Physics, Engineering Sciences, Nano Technology, Material Sciences, Polymer Science, Toxicology, Drug Safety, Clinical Research, Drug Regulatory Affairs, etc.

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